Clinical Review

Myelodysplastic Syndromes

DONALD C. DOLL, MD, *Columbia, Missouri, and* ALAN F. LIST, MD, *Tucson*

The myelodysplastic syndromes are a heterogeneous group of hematopoietic stem cell disorders characterized by dysplastic and ineffective hematopoiesis and a varying risk of transformation to acute leukemia. Although the natural history of these syndromes is variable, several factors appear to be of prognostic importance, including the French-American-British classification, the karyotype, in vitro colony formation, and others. The pathogenesis of the myelodysplastic syndrome is not known, but recent evidence suggests that alterations of cellular oncogenes may be a causative factor. There is no standard therapy for myelodysplasia, and thus novel approaches to patient management are warranted.

(Doll DC, List AF: Myelodysplastic syndromes. West J Med 1989 Aug; 151:161-167)

The myelodysplastic syndromes are a heterogeneous group of hematopoietic stem cell disorders characterized by ineffective and dysplastic hematopoiesis.[1,2] Most patients are older than 60 years and characteristically have peripheral cytopenia(s) with a normocellular or hypercellular bone marrow. Leukemic transformation is not uncommon, but even in its absence, a myelodysplastic syndrome may be a lethal hematologic disorder with death from infection and bleeding[3] arising from cytopenia or impaired function of neutrophils[4] and platelets.[5] Although this syndrome may occur as a late complication of chemotherapy or radiotherapy,[6] the cause(s) of de novo myelodysplasia remains obscure. The treatment of these syndromes remains unsatisfactory, but promising new therapeutic regimens have recently been used in an attempt to restore normal hematopoiesis.[7]

Classification and Diagnosis

Numerous terms have been applied to describe the myelodysplastic syndromes, including preleukemia, hematopoietic dysplasia, refractory anemia, refractory normoblastic anemia, refractory anemia with an excess of myeloblasts, subacute myeloid leukemia, oligoblastic leukemia, dysmyelopoietic syndromes, smoldering leukemia, myeloid dysplasia, and primary acquired panmyelopathy with myeloblastosis. Such diverse terminology and a lack of uniform criteria for these disorders have resulted in inevitable difficulties in classification and in predicting the disease outcome. In 1982 the French-American-British (FAB) Cooperative Group addressed this problem and proposed a morphologic classification system encompassing the spectrum of diseases.[1] As shown in Table 1, five subtypes of the syndromes have been described: refractory anemia; refractory anemia with ring sideroblasts; refractory anemia with an excess of blast forms; refractory anemia with an excess of blast forms in transformation; and chronic myelomonocytic leukemia. Although several investigators have questioned the need for and validity of this new scheme, it has enjoyed widespread acceptance because of its reproducibility and has been found useful for comparing studies among different institutions. The results of several recent studies that have classified their cases according to this system are given in Table 2.[3,8-18] Some investigators included cases in their analysis associated with cytotoxic chemotherapy or radiotherapy,[8,9,18] and others included only patients with de novo myelodysplasia.[3,10-17] Also, several investigators found it difficult to categorize particular patients in specific subtypes and noted that transitions and combinations existed in individual patients.[9-11,18]

The clinical diagnosis of a myelodysplastic syndrome can often be made by visually inspecting the bone marrow aspirate and peripheral blood smear and detecting various dysplastic changes in each hematopoietic lineage.[1,2,19] The examination of bone marrow specimens from trephine biopsies,[20] chromosome analysis,[13,15-17,21,22] in vitro hematopoietic stem cell assays,[16,23] and flow cytometry[24] may provide additional supportive evidence. Investigating the oncogene expression at the first clinical signs of the syndrome and throughout the progression of disease would also be of interest.[25] Such specialized investigations may be particularly useful to confirm the diagnosis in those patients with minimal hematologic or morphologic changes. Moreover, these tests may be useful in predicting the clinical outcome (vide infra).

The cytopenia(s) that direct attention to the disorder should be confirmed as a persistent feature, unassociated with any other systemic disorder such as renal or hepatic failure or ethanol abuse. Vitamin B_{12} and folate deficiency should be excluded. In addition, a detailed occupational history for exposure to potential carcinogens and a previous history of treatment with cytotoxic drugs or radiotherapy should be elicited.

Clinical and Laboratory Manifestations

The exact incidence of de novo myelodysplasia is unknown; it is not uncommon in the elderly population, however. For instance, 174 patients with the syndromes were seen at the Mayo Clinic during a three-year period.[17] Juneja

From the Department of Medicine, Division of Hematology/Medical Oncology, University of Missouri-Columbia School of Medicine, Columbia (Dr Doll), and the Section of Hematology/Oncology, Veterans Administration Medical Center, Tucson (Dr List).

Reprint requests to Donald C. Doll, MD, Department of Medicine, MA 434 Medical Sciences Bldg, One Hospital Dr, Columbia, MO 65212.

ABBREVIATIONS USED IN TEXT

CSF = colony-stimulating factor
FAB = French-American-British [Cooperative Group]
G6PD = glucose-6-phosphate dehydrogenase

and co-workers saw 118 new cases of these disorders during a similar time span compared with 126 new cases of acute myeloid leukemia.[10] The myelodysplastic syndromes occur in a middle-aged to elderly population, with the median age in most series being about 65. Cases diagnosed before age 50 are uncommon, and there is a male predominance.[1,2,16,19] Most patients are seen because of weakness, fatigue, or pallor due to anemia. Some patients seek advice because of bleeding, easy bruising, or infection. Hepatomegaly, splenomegaly, and lymphadenopathy are infrequent findings on a physical examination.

The hematologic abnormalities in these disorders have been extensively described[1,2,8-11,19] and are summarized in Table 3. It should be emphasized that such findings are pleomorphic and are not in and of themselves diagnostic; they may be susceptible to subjective interpretation, and other disorders must be excluded.

Most patients with the syndromes are anemic with an inappropriately low reticulocyte response. The erythrocytes are usually normocytic or macrocytic, although patients may present with microcytosis, hypochromia, and reticulocytosis.[26] Anisocytosis, poikilocytosis, basophilic stippling, and megaloblastoid nucleated erythrocytes may be seen. Such peripheral blood findings are characteristically associated with dyserythropoietic features in bone marrow progenitors with both nuclear and cytoplasmic abnormalities. These may include erythroid hyperplasia with megaloblastoid features, nuclear budding, multinucleation, karyorrhexis, and vacuolization of the cytoplasm. Ringed sideroblasts can usually be found in a varying proportion of normoblasts. Abnormalities of erythrocyte glycolytic enzymes,[27] increases in hemoglobin F levels,[28] alterations in blood group antigens,[29] and paroxysmal nocturnal hemoglobinuria-like defects[30] have been described. Acquired hemoglobin H disease has also been noted.[31]

Leukopenia, usually due to absolute neutropenia, is found in about half the patients at the time of diagnosis. Granulocytes may show reduced segmentation—the pseudo-Pelger-Huët abnormality—or reduced or absent granulation. Circulating myelocytes and blast cells may be detected

TABLE 1.—*Classification of the Myelodysplastic Syndromes*

FAB Classification	*Blasts in Bone Marrow, %*	*Other Findings*
Refractory anemia (RA)	<5	<1% circulating blast cells
RA with ring sideroblasts	<5	<1% circulating blast cells; 15% ring sideroblasts in bone marrow
RA with excess blasts	5-20	<5% circulating blasts
Chronic myelomonocytic leukemia	<20	1×10^9/liter monocytes and promonocytes in peripheral blood
RA with excess blasts in transformation	20-30	5% circulating blast cells; Auer rods

FAB=French-American-British

TABLE 2.—*Diagnostic Subtypes of the Myelodysplastic Syndromes*

Source	*Patients, No.*	*Refractory Anemia*	*RARS*	*CMML*	*RAEB*	*RAEB-T*
Gold et al, 1983[16]	34	2	0	10	22	0
Juneja et al, 1983[10]	118	9	43	0	66	0
Weisdorf et al, 1983[3]	74	30	23	1	9	11
Foucar et al, 1985[8]	109	13	22	11	41	22
Knapp et al, 1985[15]	167	43	38	11	69	6
May et al, 1985[11]	39	9	15	4	9	2
Tricot et al, 1985[12]	85	25	12	11	14	23
Vallespi et al, 1985[9]	101	32	15	21	12	21
Jacobs et al, 1986[17]	46	14	8	10	9	5
Kuriyama et al, 1986[14]	50	25	7	8	10	0
Yunis et al, 1986[13]	56	13	13	3	23	4
Group Français, 1987[18]	761	131	107	129	329	65
Total	1,640	346	303	219	614	159

CMML=chronic myelomonocytic leukemia, RAEB=refractory anemia with excess blast forms, RAEB-T=refractory anemia with excess blast forms in transformation, RARS=refractory anemia with ring sideroblasts

TABLE 3.—*Morphologic Abnormalities in Myelodysplastic Syndromes*

Lineage	*Peripheral Blood*	*Bone Marrow*
Erythroid	Macrocytes; ovalocytes; basophilic stippling; nucleated erythrocytes; poikilocytosis and anisocytosis; acanthocytes	Megaloblastoid erythropoiesis; nuclear budding; multinucleation; ringed sideroblasts; karyorrhexis; nuclear fragments; cytoplasmic vacuolization
Myeloid	Hypersegmentation; pseudo-Pelger-Huët anomaly; vacuolization; paramyeloid cells; abnormal or deficient granulation; nuclear tags	Defective granulation; partial maturation arrest at myelocyte stage; increase in monocytoid forms
Megakaryocytic	Agranular or giant platelets	Micromegakaryocytes; large mononuclear forms; multiple small nuclei

but generally constitute fewer than 5% of the leukocyte differential. Auer rods are rare. The neutrophil myeloperoxidase activity is decreased in some patients,[4] and there may be an increase in monocyte-specific esterase.[32] Granulocytes may also show defective phagocytosis, bactericidal activity, adhesion, and chemotaxis,[4] leading to a reduced resistance to infections. These features may have a common cytogenetic basis attributable to a partial or complete loss of chromosome 7.[33] Impaired myeloid maturation is readily detected on inspecting the bone marrow aspirate, which typically shows an increased percentage of granulocytic precursors, and a "maturation arrest" is often noted at the myelocyte stage.

Thrombocytopenia is seen in about 50% of patients with the myelodysplastic syndromes, and the platelets may be abnormal in both morphologic features and function. Abnormal megakaryocytes, including micromegakaryocytes, large mononuclear forms, and megakaryocytes with multiple small nuclei, are common bone marrow findings.[1,14] Indeed, Kuriyama and associates suggested that micromegakaryocytes detected in the marrow coupled with pseudo-Pelger-Huët anomalies in the peripheral blood smear represent the most specific features supporting the diagnosis of the syndrome.[14]

The lymphoid system may also be affected in patients with these syndromes, and it has been shown that the abnormal cells may be derived from the same clone as the pathologic erythroid and myeloid cells.[34] Lymphopenia with a reduced number of T-helper cells has been reported.[35] Natural killer cells may be reduced in number, and there may be an inadequate production of interferon and a failure of natural killer cells to respond to interferon. Abnormalities of T- and B-cell function have been noted.[36] Lastly, a high incidence of immunologic abnormalities such as monoclonal gammopathy and autoantibodies[37] and coexistent lymphoid or plasma cell neoplasms have been shown in these patients.[38]

Cytogenetic Abnormalities

Using standard techniques of karyotype analysis, clonal chromosomal aberrations have been detected in about a third to half of patients with de novo myelodysplasia.[3,12,15-17,21] Using refined chromosome banding techniques, however, Yunis and colleagues reported that 73% of patients with these syndromes had a cytogenetic defect.[13,39] Moreover, these identified prognostic subgroups of the disorder.[13,39]

The chromosome abnormalities follow a nonrandom pattern and are similar to those found in treatment-induced acute myelogenous leukemia.[21] The abnormal clone can replace normal hematopoiesis partially or completely. As shown in Table 4, the most frequent cytogenetic abnormalities in the myelodysplastic syndromes involve structural or numeric abnormalities of chromosomes 5 and 7 and trisomy 8.[21] Other findings include a reduplication of chromosome 9, expressed +9, 21 (+21), or the long arm of chromosome 1; a deletion of chromosome 20 (−20); and an isochromosome 17 (i17). Complex chromosomal abnormalities occur in some patients and are more frequent in secondary myelodysplasia.[39,40] Such cytogenetic findings support the notion that these syndromes are clonal in nature. It is noteworthy that certain chromosomal abnormalities found in acute myelocytic leukemia are rarely found in the myelodysplastic syndromes, suggesting that in patients with these aberrations, the disease did not develop from preexisting myelodysplasia.

TABLE 4.—*Frequent Chromosome Abnormalities in Myelodysplastic Syndromes**

Chromosome Abnormality	Incidence, %
−5/5q−	10-20
−7/7q−	15-25
+8	15-20
20q−	7-10

*q represents the long arm of a chromosome, + represents a duplication of a chromosome or chromosome segment, and − represents a deletion of a chromosome or chromosome segment.

These include the 8:21 translocation often found with type M2 of the FAB classification, translocation (15:17) associated with acute promyelocytic leukemia, and translocation (9:22) of chronic granulocytic leukemia.

Chromosome abnormalities in patients with the myelodysplastic syndromes may be associated with a shortened survival and an increased risk of evolving to acute leukemia.[13,16,17,22,39] Although new clonal karyotypic abnormalities have emerged in association with an increase in the percentage of blasts in the bone marrow on leukemic progression,[22] most patients with these syndromes do not show chromosome abnormalities at the time of transformation to overt acute myelocytic leukemia.[22] Of note is that specific cytogenetic changes, such as deletion in the long arm of chromosome 5 (5q−),[41] or monosomy 7 (−7),[42] may be associated with distinct clinicopathologic syndromes. Whether chromosome abnormalities are involved in the pathogenesis of myelodysplasia remains to be elucidated.

Pathogenesis

Although the cause(s) of the myelodysplastic syndromes is unknown, evidence from cytogenetic studies[21] and glucose-6-phosphate dehydrogenase (G6PD) isoenzyme analyses[34,43] indicates that they are clonal disorders of pluripotent stem cells. G6PD studies have shown that Epstein-Barr virus-transformed B lymphoblastoid lines, derived from a patient with the syndrome, showed restricted G6PD isoenzyme expression.[43] Similarly, Prchal and co-workers found that T and B lymphocytes from a patient with idiopathic sideroblastic anemia were derived from the same clone as the myeloid elements.[34] Further support for the involvement of the pluripotent stem cell is provided by reports of myelodysplasia evolving to acute lymphoblastic[44] or acute leukemia showing mixed lymphoid-myeloid features.[45]

Raskind and associates suggested that the myelodysplastic syndromes arise by a multistep process. They proposed that at least two events are involved in their pathogenesis, one promoting proliferation of a clone of genetically unstable pluripotent stem cells and another inducing chromosomal abnormalities in its descendants.[43] This sequence would explain the abrupt evolution to acute leukemia in patients after a prolonged period of apparent hematologic stability.

A multistage mechanism for inducing malignancy has been shown for various tumors in many species, and oncogenes may have an important role in the process.[46] In the mouse embryo fibroblast cell line, for example, the *ras* oncogene is unable to transform fibroblasts unless they have first entered a proliferative state. If, however, both the C-*myc* and *ras* oncogenes are transfected together, a malignant transformation results.[47] Thus, single insults by themselves do not

produce a malignant transformation, but a succession of two events may.[46]

Although the significance of chromosomal changes in malignant cells is still not fully understood, there is increasing evidence that chromosomal rearrangements are instrumental in activating cellular oncogenes.[48] As noted earlier, karyotypic aberrations are frequent in the myelodysplastic syndromes and most commonly involve chromosomes 5, 7, and 8. Chromosome 5 carries two known oncogenes, c-*fos* and c-*fms,* on its long arm; chromosome 7 contains the oncogene *erb*$_\beta$; and chromosome 8, c-*myc.*[49] Furthermore, three oncogenes—*ras, myc,* and *fos*—have been directly implicated in growth factor-mediated signaling mechanisms,[50] and, as suggested by Duel and Huang,[51] any genes that code for proteins influencing the cellular response to growth factors represent potential oncogenes. Abnormalities in the expression of these genes, whether resulting from deletion, duplication, abnormal activation, suppression, or mutation, can result in a change in the control of proliferation, which may contribute to the malignant process. Indeed, an activated N-*ras* oncogene in patients with deletion of the long arm of chromosome 5 has been shown during a leukemic progression from myelodysplasia.[52]

Thus, an initiating event may be speculated in these syndromes, perhaps activation of a cellular oncogene, that triggers the proliferation of an abnormal clone. The expanding clone may become immortalized by the loss of normal control mechanisms governing the synthesis of DNA or autonomy from normal growth inhibitory factors (or both). Results of in vitro studies indicate that the malignant clone may also inhibit normal hematopoiesis. Depending on the genetic instability and proliferative capabilities of the clone, myelodysplasia may progress to overt acute myelocytic leukemia. The role of oncogenes, antioncogenes, growth factors, chromosomal aberrations, and stromal cells in the pathogenesis of these disorders needs further evaluation.

Management

The treatment of the myelodysplastic syndromes has in general been disappointing. Most patients with these disorders are elderly and may have other morbid medical problems that complicate therapeutic decisions. Because these syndromes comprise a heterogeneous group of disorders with varying clinical courses, a period of observation with close monitoring of blood cell counts and sequential marrow examinations is the mainstay of the initial management. Some patients, particularly those with refractory anemia or refractory anemia with ring sideroblasts, may have an indolent course, and no treatment may be required. Other patients may require blood transfusions to alleviate the symptoms of anemia or antibiotics for internal infection. For those patients who have an aggressive clinical course, however, more intensive therapy should be considered.

Despite evidence of megaloblastosis, initial supplementation with vitamin B_{12} or folic acid is generally not beneficial. Although a subset of patients with sideroblastic anemia may respond to the administration of pyridoxine hydrochloride or pyridoxal-5-phosphate,[53] most patients show no improvement. Nevertheless, a therapeutic trial of pyridoxine, 300 mg daily, should be considered in patients with sideroblastic anemia. Similarly, corticosteroid therapy is not useful in most patients, although in vitro cortisol-enhanced colony growth may identify a small subset of patients who might benefit from such therapy.[54] In view of their possible added toxicity and the low frequency of response, corticosteroids should not be used as empiric therapy.

The use of androgens has also proved ineffective in these patients.[55] Danazol, a synthetic attenuated androgen, has recently been reported to have activity in patients occasionally seen who have this syndrome and concomitant immune thrombocytopenia or hemolysis.[56] In the usual patient with a myelodysplastic syndrome who has marrow dysfunction, we and others have not found this agent to be useful.[57,58]

13-*cis*-Retinoic acid, a stereoisomer of retinoic acid, has also been used in patients with this syndrome.[59–63] In vitro studies have shown that retinoic acid inhibits tumor cell growth and also induces differentiation in various tumor cell lines,[64] including the human promyelocytic leukemia cell line HL-60.[65] Retinoids stimulate the growth of normal erythroid progenitors in vitro and increase granulopoiesis.[65] Based on these findings, several uncontrolled clinical trials using 13-*cis*-retinoic acid in these patients have been reported.[59–62] In general, the studies have shown a low response rate, and all responses were partial, of short duration, and accompanied by moderate dermatologic or hepatic toxicity.[59–62] Moreover, the drug had to be given for at least three weeks and sometimes several months before a response was seen. Recently a randomized study comparing the use of 13-*cis*-retinoic acid with placebo in patients with this disorder showed no beneficial effect.[63] Hence, *cis*-retinoic acid is not recommended for routine clinical practice. The efficacy of other retinoids with less toxicity merits evaluation.

Intensive cytotoxic treatment, such as that used in cases of acute leukemia, has also been employed partially in patients with high-risk subtypes, such as refractory anemia with excess blast forms, with blast forms in transformation, and chronic myelomonocytic leukemia.[66] The regimens used varied, but most included cytarabine (cytosine arabinoside) hydrochloride and an anthracycline. The response rate ranged from 15% to 53%, with complete remission seen primarily in those patients younger than 50 years.[66,67] In the series reported by Tricot and Boogaerts, six of seven patients younger than 50 years achieved complete remission compared with only two of eight patients in the older age group.[67] Of note is that all eight patients had a completely normal karyotype at the time of complete bone marrow remission. Thus aggressive combination chemotherapy may be of value in younger patients with specific subtypes of primary myelodysplasia. Whether such therapy has a significant impact on the survival of these patients has not yet been determined.

Most recently, several investigators have used low doses of cytarabine in the treatment of these syndromes.[68–71] The dosages ranged from 5 to 20 mg per m^2 of body surface daily by continuous intravenous infusion or subcutaneous injection. Although notable responses were recorded in approximately 60% of patients, they were generally partial and of short duration, usually not exceeding five months. Second and third responses may be achieved with the same regimen after an initial relapse.[68] Even with low-dose regimens, however, toxicity was substantial, with about 50% of patients experiencing a major complication, such as sepsis or hemorrhage.

Whether low-dose cytarabine acts by inducing cellular differentiation or by a cytotoxic mechanism is controversial.[72] When an abnormal clone can be identified by cytogenetic studies, treatment with low-dose cytarabine (ara-C)

results in suppression of this clone rather than maturation,[73] suggesting that a response is achieved primarily by a cytotoxic effect rather than differentiation. Any advantage of low-dose ara-C over standard-dose cytarabine regimens remains to be determined. In light of its considerable toxicity and short duration of response, the use of low-dose ara-C cannot be recommended for routine clinical practice.[74]

Additional therapeutic methods that merit consideration in the treatment of these syndromes include bone marrow transplantation,[75] azacitidine (5-azacytidine), biologic response modifiers,[76] vitamin D_3,[77] haem arginate,[78] and colony-stimulating factors (CSFs).[79] The recent cloning of CSFs has made large amounts of the purified protein available for investigational use.[80,81] Preliminary results suggest that granulocyte CSFs can induce the differentiation of myeloid leukemia cells in vitro[81] and that infusing human granulocyte-macrophage CSFs into primates stimulates a pronounced leukocytosis and reticulocytosis.[82] A phase I study using recombinant granulocyte-macrophage CSFs in patients with the myelodysplastic syndromes showed short-term improvement in hematologic variables in some patients.[83] Future trials in these syndromes should evaluate combinations of differentiating agents with cytotoxic drugs, interferons, tumor necrosis factor, and colony-stimulating factors.[84-89]

Course and Prognosis

The natural history of this disorder varies widely, with some patients having an indolent clinical course, whereas others will succumb during the first year.[3,9,12] Although acute leukemia will eventually develop in a substantial portion of patients (12% to 38%), an even larger percentage (30% to 63%) will succumb to complications resulting from bone marrow failure.[3,12] In rare cases, myelodysplasia will terminate in acute myelofibrosis[10] or in a syndrome simulating malignant histiocytosis.[90]

Several factors have been reported to influence the prognosis in these syndromes. The FAB classification appears to be the most important prognostic marker. For example, concomitant neutropenia, thrombocytopenia, or both are less prevalent in patients with refractory anemia with ring sideroblasts, and the disease seldom evolves into acute leukemia. The median survival in patients with this subtype generally exceeds 60 months.[8,12,91] In contrast, chronic myelomonocytic leukemia is associated with a poor prognosis, with a median survival of about 18 months.[91,92] For the other three subtypes, the rising marrow blast-cell number is associated with an increased mortality and a heightened risk of leukemic transformation.[8-13,91,93] Hence, the median survival for these disorders ranges from greater than 30 months in refractory anemia, to 11 months in refractory anemia with an excess of blast forms, and 5 months in refractory anemia with an excess of blast forms in transformation.[8-13,91]

According to most investigators, karyotypic findings provide an additional prognostic measure.[13,15-17,39,93] An abnormal karyotype, in particular complex chromosome abnormalities, confers a higher risk of leukemic evolution and therefore a shorter survival.[13,15-17,39,93] In this regard, Yunis and colleagues recently proposed prognostic subgroups of the myelodysplastic syndromes based on cytogenetic findings.[39] They reported that patients with a normal karyotype or isolated monosomy 5 had a relatively favorable prognosis. In contrast, patients with trisomy 8, monosomy 7, or complex defects had a poor prognosis. In addition to karyotype analysis, determining the DNA content of bone marrow cells by flow cytometry may also yield important prognostic information.[24]

A third discriminatory factor is based on the peripheral blood findings, with multilineage defects associated with a poor prognosis.[3,8,10,12,91,93] Mufti and co-workers suggested a scoring system for predicting disease outcome.[91] A score of 1 is assigned for each of the following presenting features: bone marrow blasts of more than 0.05 (5%), platelets of less than 100×10^9 per liter (100,000 per μl), neutrophils of less than 2.5×10^9 per liter (2,500 per μl), and hemoglobin less than 6.21 mmol per liter (10 grams per dl). Patients with a score of 4 had a median survival of only 8.5 months, those with a score of 0 or 1 had a median survival of 62 months, and those with a score of 2 or 3 had a median survival of 22 months. Other investigators have also proposed a scoring system for these disorders.[94,95]

Another prognostic factor is the in vitro myeloid growth pattern. Patients with nonleukemic in vitro growth patterns have a 21% to 40% incidence of transformation to acute leukemia and a median survival of 9 to 50 months. In contrast, persons with leukemic growth patterns have had a 50% to 80% incidence of transformation and 5 to 10 months' median survival.[23] There is no correlation of in vitro growth patterns with the FAB classification.

Other factors that have been reported to adversely affect survival include a high percentage of abnormal metaphases,[16] the presence of large clusters or an inability to culture granulocyte-macrophage colonies,[36,93] the number of ringed sideroblasts,[96] and the central clustering of immature myeloid precursors in the bone marrow matrix rather than adhering to the endosteal surface.[97] Such prognostic factors should be considered in choosing therapy for patients with the myelodysplastic syndromes.

REFERENCES

1. Bennett JM, Catovsky D, Daniel MT, et al: Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982; 51:189-199

2. Greenberg PL: The smoldering myeloid leukemic states: Clinical and biological features. Blood 1983; 61:1035-1044

3. Weisdorf DJ, Oken MM, Johnson GJ, et al: Chronic myelodysplastic syndrome: Short survival with or without evolution to acute leukemia. Br J Haematol 1983; 55:691-700

4. Boogaerts MA, Nelissen V, Roelant C, et al: Blood neutrophil function in primary myelodysplastic syndromes. Br J Haematol 1983; 5:217-227

5. Russell NH, Keenan JP, Bellingham AJ: Thrombocytopathy in preleukemia: Association with a defect of thromboxane A_2 activity. Br J Haematol 1979; 41:417-425

6. Levine EG, Bloomfield CD: Secondary myelodysplastic syndromes and leukaemias. Clin Haematol 1986; 15:1037-1080

7. Tricot GJ, Lauer RC, Appelbaum FR, et al: Management of the myelodysplastic syndromes. Semin Oncol 1987; 14:444-453

8. Foucar K, Langdon RM, Armitage JO, et al: Myelodysplastic syndromes—A clinical and pathologic analysis of 109 cases. Cancer 1985; 56:553-561

9. Vallespi T, Torrabadella M, Julia A, et al: Myelodysplastic syndromes: A study of 101 cases according to the FAB classifications. Br J Haematol 1985; 61:83-92

10. Juneja SK, Imbert M, Jouault H, et al: Haematological features of primary myelodysplastic syndromes (PMDS) at initial presentation: A study of 118 cases. J Clin Pathol 1983; 36:1129-1135

11. May SJ, Smith SA, Jacobs A, et al: The myelodysplastic syndrome: Analysis of laboratory characteristics in relation to the FAB classification. Br J Haematol 1985; 59:311-319

12. Tricot G, Vlietinck R, Boogaerts MA, et al: Prognostic factors in the myelodysplastic syndrome: Importance of initial data on peripheral blood counts, bone marrow cytology, trephine biopsy and chromosome analysis. Br J Haematol 1985; 60:19-32

13. Yunis JJ, Rydell RE, Oken MM, et al: Refined chromosome analysis as an independent prognostic indicator in de novo myelodysplastic syndromes. Blood 1986; 67:1721-1730

14. Kuriyama K, Tomonaga M, Matsuo T, et al: Diagnostic significance of detecting pseudo-Pelger-Huët anomalies and micro-megakaryocytes in myelodysplastic syndrome. Br J Haematol 1986; 63:665-669

15. Knapp RH, Dewald GW, Pierre RV: Cytogenetic studies in 174 consecutive

patients with preleukemic or myelodysplastic syndromes. Mayo Clin Proc 1985; 60:507-516

16. Gold EJ, Conjalka M, Pelus IM, et al: Marrow cytogenetic and cell-culture analyses of the myelodysplastic syndromes: Insights to pathophysiology and prognosis. J Clin Oncol 1983; 1:627-634

17. Jacobs RH, Cornbleet MA, Vardiman JW, et al: Prognostic implications of morphology and karyotype in primary myelodysplastic syndromes. Blood 1986; 67:1765-1772

18. Group Français de Morphologie Hematologique: French registry of acute leukemia and myelodysplastic syndromes. Cancer 1987; 60:1385-1394

19. Koeffler HP, Golde DW: Human preleukemia. Ann Intern Med 1980; 93:347-353

20. Tricot G, De Wolf-Peeters C, Hendricks B, et al: Bone marrow histology in myelodysplastic syndromes—I. Histological findings in myelodysplastic syndromes and comparison with bone marrow smears. Br J Haematol 1984; 57:423-430

21. Nowell PC: Cytogenetics of preleukemia. Cancer Genet Cytogenet 1982; 5:265-278

22. Tricot G, Boogaerts MA, De Wolf-Peeters C, et al: The myelodysplastic syndromes: Different evolution patterns based on sequential morphological and cytogenetic investigations. Br J Haematol 1985; 59:659-670

23. Greenberg PL: In vitro culture techniques defining biological abnormalities in the myelodysplastic syndromes and myeloproliferative disorders. Clin Haematol 1986; 15:973-993

24. Clark R, Peters S, Hoy T, et al: Prognostic importance of hypodiploid hemopoietic precursors in myelodysplastic syndromes. N Engl J Med 1986; 314:1472-1475

25. Tricot G, Mecucci C, Van den Berghe H: Evolution of the myelodysplastic syndromes. Br J Haematol 1986; 63:609-614

26. Tulliez M, Testa U, Rochant H: Reticulocytosis, hypochromia, and microcytosis: An unusual presentation of the preleukemic syndrome. Blood 1982; 59:293-299

27. Valentine WN, Konrad PN, Paglia DE: Dyserythropoiesis, refractory anemia, and 'preleukemia': Metabolic features of the erythrocytes. Blood 1973; 41:857-875

28. Rochant H, Dreyfus B, Bouguerra M, et al: Refractory anaemias, preleukaemic conditions, and foetal erythropoiesis. Blood 1972; 39:721-726

29. Levine MN, Kuhns WK, Bolk TA, et al: Acquired alteration in the expression of blood groups in a patient with sideroblastic anemia and chronic renal failure. Transfusion 1984; 24:8-12

30. Hauptmann G, Sondag D, Lang JM, et al: 'False positive' acidified serum test in a preleukaemic dyserythropoiesis. Acta Haematol 1978; 59:73-79

31. Boehme WM, Piira TA, Kurnick JE, et al: Acquired hemoglobin H in refractory sideroblastic anemia: A preleukemic marker. Arch Intern Med 1978; 136:603-606

32. Scott CS, Cahill A, Bynoe AG, et al: Esterase cytochemistry in primary myelodysplastic syndromes and megaloblastic anaemias: Demonstration of abnormal staining patterns associated with dysmyelopoiesis. Br J Haematol 1983; 55:411-418

33. Ruutu P, Ruutu T, Repo H, et al: Defective neutrophil migration in monosomy-7. Blood 1981; 58:739-745

34. Prchal JT, Throckmorton DW, Carroll AJ, et al: A common progenitor for human myeloid and lymphoid cells. Nature 1978; 274:590-591

35. Bynoe AG, Scott CS, Ford P, et al: Decreased T-helper cells in the myelodysplastic syndromes. Br J Haematol 1983; 54:97-102

36. Bateman OA, Shevitz J, Traub UC, et al: Lymphocyte interleukin 2 production and responsiveness are altered in patients with primary myelodysplastic syndrome. Blood 1987; 70:494-500

37. Mufti GJ, Figes A, Hamblin TJ, et al: Immunologic abnormalities in myelodysplastic syndromes—I. Serum immunoglobulin and autoantibodies. Br J Haematol 1986; 63:143-147

38. Copplestone JA, Mufti GJ, Hamblin TJ, et al: Immunological abnormalities in myelodysplastic syndromes—II. Coexistent lymphoid or plasma cell neoplasms: A report of 20 cases unrelated to chemotherapy. Br J Haematol 1986; 63:149-159

39. Yunis JJ, Lobell M, Arnesen MA, et al: Refined chromosome study helps define prognostic subgroups in most patients with primary myelodysplastic syndrome and acute myelogenous leukaemia. Br J Haematol 1988; 68:189-194

40. Whang-Peng J, Young RC, Lee EC, et al: Cytogenetic studies in patients with secondary leukaemia/dysmyelopoietic syndrome after different treatment modalities. Blood 1988; 71:403-414

41. Van den Berghe H, Cassiman J, David G, et al: Distinct haematological disorder with deletion of long arm of No. 5 chromosome. Nature 1974; 251:437-438

42. Kere J, Ruutu T, de la Chapelle A: Monosomy 7 in granulocytes and monocytes in myelodysplastic syndrome. N Engl J Med 1987; 316:499-503

43. Raskind WH, Tirumali N, Jacobson R, et al: Evidence for a multistep pathogenesis of a myelodysplastic syndrome. Blood 1984; 63:1318-1323

44. Barton JC, Conrad ME, Parmley RT: Acute lymphoblastic leukemia in idiopathic refractory sideroblastic anemia: Evidence for a common lymphoid and myeloid progenitor cell. Am J Hematol 1980; 9:109-115

45. Erndani S, Chan LC, Halil O, et al: Acute biphenotypic leukaemia (myeloid and null-ALL type) supervening in a myelodysplastic syndrome. Br J Haematol 1985; 61:525-529

46. Land H, Parada LF, Weinberg RA: Cellular oncogenes and multistep pathogenesis. Science 1983; 222:771-778

47. Land H, Parada LF, Weinberg RA: Tumorigenic conversion of primary embryo fibroblasts requires at least two cooperating oncogenes. Nature 1983; 304:596-602

48. Robertson M: Message of *myc* in context. Nature 1984; 309:585-587

49. McKusick VA: The human gene map, 1 December 1984. Clin Genet 1985; 27:207-239

50. Sporn MB, Roberts AB: Autocrine growth factors and cancer. Nature 1985; 313:745-747

51. Duel TX, Huang JS: Roles of growth factor activities in oncogenes. Blood 1984; 64:951-958

52. Hirai H, Okada M, Mizoguchi H, et al: Relationship between an activated N-*ras* oncogene and chromosomal abnormality during leukemic progression from myelodysplastic syndrome. Blood 1988; 71:256-258

53. Mason DY, Emerson PM: Primary acquired sideroblastic anaemia: Response to treatment with pyridoxal-5-phosphate. Br Med J 1973; 1:389-390

54. Bagby GC Jr, Gabourel JD, Linman JW: Glucocorticoid therapy in the preleukemic syndrome (hemopoietic dysplasia)—Identification of responsive patients using in vitro techniques. Ann Intern Med 1980; 92:55-58

55. Najean Y, Pecking A: Refractory anaemia with excess of myeloblasts in the bone marrow: A clinical trial of androgens in 90 patients. Br J Haematol 1977; 37:25-33

56. Cines DB, Cassileth PA, Kiss JE: Danazol therapy in myelodysplasia. Ann Intern Med 1985; 103:58-60

57. Doll DC, Ringenberg QS, Yarbro JW: Danazol therapy in acquired idiopathic sideroblastic anaemia. Acta Haematol 1987; 77:170-171

58. Buzaid AC, Garewal HS, Lippman SM, et al: Danazol in the treatment of myelodysplastic syndromes (Abstr). Clin Res 1987; 35:186A

59. Gold EJ, Mertelsmann RH, Itri LM, et al: Phase I clinical trial of 13-*cis*-retinoic acid in myelodysplastic syndrome. Cancer Treat Rep 1983; 67:981-986

60. Greenberg BR, Durie BGM, Barnett TC, et al: Phase I-II study of 13-*cis*-retinoic acid in myelodysplastic syndrome. Cancer Treat Rep 1985; 69:1369-1374

61. Picozzi VJ, Swanson GF, Morgan R, et al: 13-*cis*-Retinoic acid treatment for myelodysplastic syndromes. J Clin Oncol 1986; 4:589-595

62. Clark RE, Jacobs A, Lash CJ, et al: Effect of 13-*cis*-retinoic acid on survival of patients with myelodysplastic syndrome. Lancet 1987; 1:763-765

63. Koeffler HP, Heitjan D, Mertelsmann R, et al: Randomized study of 13-*cis*-retinoic acid *v* placebo in the myelodysplastic disorders. Blood 1988; 71:703-708

64. Meyskens FL Jr, Fuller BB: Characterization of the effects of different retinoids on the growth and differentiation of a human melanoma cell line and selected subclones. Cancer Res 1980; 40:2194-2196

65. Breitman TE, Selonick SE, Collins SJ: Induction of the human promyelocytic leukemia cell line (HL-60) by retinoic acid. Proc Natl Acad Sci USA 1980; 77:2936-2940

66. Armitage JO, Dick FR, Needleman SW, et al: Effect of chemotherapy for the myelodysplastic syndrome. Cancer Treat Rep 1981; 65:601-605

67. Tricot G, Boogaerts MA: The role of aggressive chemotherapy in the treatment of the myelodysplastic syndromes. Br J Haematol 1986; 63:477-483

68. Griffin JD, Spriggs D, Wisch JS, et al: Treatment of preleukemic syndromes with continuous intravenous infusion of low-dose cytosine arabinoside. J Clin Oncol 1985; 3:982-991

69. Tricot G, DeBock R, Dekker AW, et al: Low-dose cytosine arabinoside in myelodysplastic syndromes. Br J Haematol 1984; 58:231-240

70. Winter JN, Variakojis D, Gaynor ER, et al: Low-dose cytosine arabinoside (ara-C) therapy in the myelodysplastic syndromes and acute myeloid leukemia. Cancer 1985; 56:443-449

71. Mufti GJ, Oscier DG, Hamblin TJ, et al: Low doses of cytarabine in the treatment of myelodysplastic syndrome and acute myeloid leukemia. N Engl J Med 1983; 309:1653-1654

72. Desforges JF: Cytarabine: Low-dose, high-dose, no dose? (Editorial) N Engl J Med 1983; 309:1637-1639

73. Spiers ASD, Chikkappa G, Lorch CA: Myelodysplastic syndrome: Cytogenetic changes before and after response to low dose ara-C (Abstr). Blood 1984; 64 (suppl 1):174A

74. Cheson BD, Jasperse DM, Simon R, et al: A critical appraisal of low-dose cytosine arabinoside in patients with acute non-lymphocytic leukemia and myelodysplastic syndromes. J Clin Oncol 1986; 4:1857-1864

75. Appelbaum FR, Storb R, Ramberg RE, et al: Allogeneic marrow transplantation in the treatment of preleukemia. Ann Intern Med 1984; 100:689-693

76. Blok WL, Lowenberg B, Sizoo W: Disappearance of trisomy 8 after alpha-2 interferon in a patient with myelodysplastic syndrome (Letter). N Engl J Med 1988; 318:787-788

77. Koeffler HP, Hirji K, Itri L: 1,25-dihydroxy-vitamin D_3: In vivo and in vitro effects on human preleukemic and leukemic cells. Cancer Treat Rep 1985; 69:1399-1407

78. Ruutu T, Volin L, Tenhunen R: Haem arginate as a treatment for myelodysplastic syndromes. Br J Haematol 1987; 65:425-428

79. Metcalf D: The molecular biology and functions of the granulocyte-macrophage colony stimulating factors. Blood 1986; 67:257-267

80. Wong GG, Witek JS, Temple PA, et al: Human GM-CSF: Molecular cloning of the complementary DNA and purifications of the natural and recombinant proteins. Science 1985; 228:810-815

81. Souza LM, Boone TC, Gabrilowe J, et al: Recombinant human granulocyte colony-stimulating factor: Effects on normal and leukemic myeloid cells. Science 1986; 232:61-65

82. Donahue RE, Wang EA, Stone DK, et al: Stimulation of hematopoiesis in primates by continuous infusion of recombinant human GM-CSF. Nature 1986; 321:872-875

83. Vadhan-Raj S, Keating M, LeMaistre A, et al: Effects of recombinant human granulocyte-macrophage colony-stimulating factor in patients with myelodysplastic syndromes. N Engl J Med 1987; 317:1545-1552

84. Trinchieri G, Rosen M, Perussia B: Retinoic acid cooperates with tumor necrosis factor and immune interferon in inducing differentiation and growth inhibition of the human promyelocytic leukemic cell line HL-60. Blood 1987; 69:1218-1224

85. Hemmi H, Breitman TR: Combinations of recombinant human interferons and retinoic acid synergistically induce differentiation of the human promyelocytic leukemia cell line HL-60. Blood 1987; 69:501-507

86. Zuckerman SH, Surprenant YM, Tang J: Synergistic effect of granulocyte-macrophage colony-stimulating factor and 1,25-dihydroxyvitamin D_3 on the differentiation of the human monocytic cell line U937. Blood 1988; 71:619-624

87. Clark RE, Ismail SAD, Jacobs A, et al: A randomized trial of 13-*cis*-retinoic acid with or without cytosine arabinoside in patients with the myelodysplastic syndrome. Br J Haematol 1987; 66:77-83

88. Tobler A, Munker R, Heitjan D, et al: In vitro interaction of recombinant tumor necrosis factor α and all-*trans*-retinoic acid with normal and leukemic hematopoietic cells. Blood 1987; 70:1940-1946

89. Weinberg JB, Larrick JW: Receptor-mediated monocytoid differentiation of human promyelocytic cells by tumor necrosis factor: Synergistic actions with interferon-γ and 1,25-dihydroxy vitamin D_3. Blood 1987; 70:994-1002

90. Doll DC, Grogan TM, Greenberg BR: Chronic myelomonocytic leukemia terminating as malignant histiocytosis. Hematol Pathol 1987; 1:183-189

91. Mufti GJ, Stevens JR, Oscier DG, et al: Myelodysplastic syndromes: A scoring system with prognostic significance. Br J Haematol 1985; 59:425-433

92. Solal-Celigny P, Desaint B, Herrera A, et al: Chronic myelomonocytic leukemia according to FAB classification: Analysis of 35 cases. Blood 1984; 63:634-638

93. Coiffier B, Adeleine P, Viala JJ, et al: Dysmyelopoietic syndrome: A search for prognostic factors in 193 patients. Cancer 1983; 52:83-90

94. Varela BL, Chuang C, Woll JE, et al: Modifications in the classification of primary myelodysplastic syndromes: The addition of a scoring system. Hematol Oncol 1985; 3:55-63

95. Doll DC, Taylor HM, Caldwell CW, et al: Myelodysplastic syndrome: Prospective evaluation of 51 patients using the Dutcher scoring system. Acta Haematol 1989; 81:86-90

96. Vandermolen L, Rice L, Rose MA, et al: Ringed sideroblasts in primary myelodysplasia—Leukemic propensity and prognostic factors. Arch Intern Med 1988; 148:653-656

97. Tricot G, De Wolf-Peeters C, Vlietinck R, et al: Bone marrow histology in myelodysplastic syndromes—II. Prognostic value of abnormal localization of immature precursors in MDS. Br J Haematol 1984; 58:217-225

Pediatric Fluid Loss

ONE PRETTY GOOD SIGN of how sick children are happens to be their capillary refill. We all know about capillary refill in a child. You squeeze a thumbnail and you say "capillary refill," and by the time you've said the last "l," the fingernail should be red again. If you press the fingernail, release it, say "capillary refill" and it's still white, this child probably has a very low blood pressure level and is verging on shock. So, always press on the child's fingernail when you are trying to estimate fluid loss.

—WILLIS A. WINGERT, MD

Extracted from *Audio-Digest Family Practice,* Vol. 36, No. 41, in the Audio-Digest Foundation's series of tape-recorded programs. For subscription information: 1577 E Chevy Chase Dr, Glendale, CA 91206